R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_8, R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, $R_{32}C=O$, $R_{33}SO_2$, hydroxy, O-alkyl or O-substituted alkyl; and

the pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and steroisomers thereof[,];

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and [R7] $\underline{R_7}$ are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

Z_1 and Z_2 are CH_2; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above

are excluded.

REMARKS

Rejection For Improper Markush Group

Claims 1-6 have been rejected for containing allegedly improper Markush grouping. The Office Action states that the recited compounds contain a variable core, thus rendering these claims improper. Applicants respectfully point out that, in addition to the common utility of the recited compounds referred to as epothilones, these compounds also share a common structural feature that is key in this class of compounds, which are known cytotoxic agents.

It is recognized by the Patent Office that "unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." *Manual of Patent Examining Procedure* (M.P.E.P.), § 803.2, at page 800-4. All that is essential is that the compounds within a Markush group have a significant structural feature in common and that the

compounds have a common utility. It is sufficient that the common structural feature be essential to the common utility. That is the case here. The claimed epothilones have a common structural feature (*i.e.*, a 16-membered ring) that is significant, as this ring system represents the bulk of the macrolides' framework. The art skilled recognize that this 16-membered ring is characteristic of epothilone molecules. Further, this feature is essential to the function of the epothilones as cytotoxic agents. Therefore, according to the M.P.E.P., the epothilone compounds encompassed by claims 1-6 would not lack unity of invention. It is, thus, respectfully requested that this rejection be withdrawn.

Claim Rejection Under 35 U.S.C. § 112, ¶ 1

Claim 4 stands rejected under 35 U.S.C. § 112, ¶ 1, for alleged lack of enablement. Applicants respectfully request reconsideration of this rejection as there is no reason of record to believe that those skilled in the art would not be able to practice the claimed invention.

The first paragraph of § 112 requires that the disclosure of a patent application be such that persons skilled in the art, having read the patent application, would be able to practice the invention described in the claims. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). There is no legal requirement that this be done in any particular manner. An enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology. *In re Marzocchi*, 169 U.S.P.Q. 367 9C.C.P.A. 1971).

When rejecting a claim under the enablement requirement of § 112, the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the Examiner must provide evidence or technical reasoning substantiating those doubts. *Id.*; and *Manual of Patent Examining Procedure*, § 2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, at 1513; *In re Marzocchi*, at 369.

Significantly, the Office Action fails to provide any facts indicating a reason to doubt that Applicants' disclosure would enable those skilled in the art to practice the claimed

invention. The Office Action appears to assert that Applicants have not enabled use of the claimed compounds for treating cancer because "remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer." Significantly, however, there is no reason of record to believe that the recited compounds will not be useful in the treatment of multiple tumor types. There is no legal requirement that Applicants provide data as to every tumor type treated with a claimed compound. All that is necessary is that it be credible to those skilled in the art that the claimed compounds can be used to treat cancer. The mere possibility that a compound may not inhibit a specific tumor does not preclude the issuance of broad claims. Partial success in achieving a useful result is sufficient for patentability. *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

In view of the current state of the art, a practitioner having ordinary skill in the art would not consider inhibition of tumors to be incredible as may have been thought in the past. That is the case here as epothilones are well recognized as a class of anitumor agents. Contrary to the view expressed in the Office Action, relative to the difficulty of the task of treating cancer, the level of skill in this art is recognized as being highly competent. Accordingly, it cannot be taken for granted, in the absence of any evidence, that claim 4 lacks enablement.

Moreover, the specification sufficiently supports the claimed method of treating cancer. For example, on page 1, it is stated that the cytotoxic activity of the compounds of the present invention is associated with their microtubule-stabilizing effects. Further, on page 8, it is elaborated that microtubule-stabilizing agents are useful as therapeutics for abnormal proliferative diseases, which is known in the art. Furthermore, on page 9, it is stated that the claimed compounds inhibit tumor angiogenesis, thereby affecting abnormal cellular proliferation.

The Office Action provides no evidence to suggest that the claimed utility of treating cancer is in dispute by those of ordinary skill in the art. Specifically, there is no cited literature which raises questions about the anticipated use of Applicants' claimed compounds for treating cancer based upon the biological properties described in the specification. The Office Action does not present any proof that would lead one of skill in the art to doubt the objective truth as to the utility of the claimed compounds in the treatment of cancer. It is, therefore, respectfully requested that this rejection be withdrawn.

Claim Rejection Under 35 U.S.C. § 112, ¶ 2

Claims 1 and 3-6 stand rejected for allegedly being indefinite.

The Office Action states that claims 1 and 4-6 are indefinite because the definition of Y contains a group with an unsatisfied valency. Applicants have amended claim 1 to delete "NOR_{19}" and insert "$NHOR_{19}$" instead. Accordingly, this rejection is now moot.

Next, the Office Action states that claims 1 and 4-6 are indefinite because, in the proviso of claim 1, reference is made to R7. Applicants have amended claim 1 to replace "R7" with "R_7." Accordingly, this rejection is now moot.

Furthermore, the Office Action states that claim 3 is indefinite because it includes a compound that is excluded by the proviso in claim 1. Applicants disagree because in the compound on page 67, lines 20-22, W is NH. Accordingly, as the proviso in claim 1 requires W to be O, the compound on page 67 (lines 20-22) is not excluded by the proviso in claim 1. It is, therefore, respectfully requested that this rejection be withdrawn

The Office Action also states that claim 6 is indefinite because undue experimentation would be required to determine which disease responds to a claimed compound. Applicants respectfully disagree because it is known to those of skill in the art that inhibition of angiogenesis arrests cellular proliferation. Making a determination of whether a disease responds to a specific compound is well within the level of skill in the art and constitutes routine experimentation. Those of skill in the art would not require an exhaustive recitation of the diseases that may be affected by inhibition of angiogenesis.

Moreover, making determinations pertaining to dosage, dosing regimen, potency, route of administration and combination with other drugs is nothing more than routine experimentation. These studies are routinely performed by the art skilled in identifying compounds for treating diseases. This in no way constitutes undue experimentation, as suggested in the Office Action, given the level of skill in the art. Accordingly, it is respectfully requested that this rejection be withdrawn.

Claim Rejection Under 35 U.S.C. § 102(b)

Claims 1 and 4-6 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Balog *et al.* (the Balog reference). The Office Action states that the Balog reference teaches the claimed compounds. Applicants respectfully disagree because the Balog

reference describes lactones while the corresponding claimed compounds are lactams. Such a lactam moiety is lacking in the compounds disclosed in the Balog reference. Specifically, the proviso in claim 1 of the present application clearly excludes compounds wherein W is O, G is a 1-methyl-2-(substituted-4-thiazolyl)ethenyl moiety, and R_3, R_4 and R_6 are methyl substituents. Accordingly, this rejection is improper and ought to be withdrawn.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 1 and 2 stand rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Höfle *et al.* (WO 97/19086; the Höfle reference). Applicants respectfully disagree with the view elaborated in the Office Action because it cannot be known *a priori* how a substituent will affect activity of the epothilone derivative.

The present invention is directed to epothilone derivatives wherein the macrolide ring structure includes a lactam moiety when R_3, R_4 and R_6 are methyl substituents and G is a 1-methyl-2-(substituted-4-thiazolyl)ethenyl moiety. Similar epothilone derivatives bearing a lactone ring are unambiguously excised from the scope of claim 1 by a proviso which states, in part, that compounds "wherein W and X are both O..... are excluded." To the contrary, compounds disclosed in the Höfle reference are lactones, not lactams. This is a significant difference because the activity of epothilones is known to be sensitive to even minor changes in structure. This is clearly evident from the numerous analogs included in the review authored by Nicolaou *et al.* (Angew. Chem., Int. Ed., 1998, 37, 2014; the Nicolaou reference), which was cited on Form 1449 and is also provided herewith. For example, on page 2034, it is shown that when a hydroxymethyl substitutuent is replaced with a methoxymethyl substituent, tubulin polymerization decreases from 29% to 6% (compare compounds 268 and 272). Furthermore, when fluoromethyl is replaced with iodomethyl, tubulin polymerization decreases from 93% to 41% (compare compounds 274 and 276). Accordingly, it is plainly evident that even the smallest quantum of change significantly affects the activity of epothilone derivatives.

The Office Action states that one "would have been motivated to select.....ethyl" (Office Action, page 8), thereby suggesting that it would have been obvious to try modifying the teachings of the Höfle reference. However, this "obvious to try" standard is not the proper test of obviousness. The mere ***possibility*** that the prior art may be modified does

not itself provide the requisite motivation to do so. *In re Dien*, 152 U.S.P.Q. 550 (C.C.P.A. 1967) (incentive to seek improvement of existing process held not to render change made by applicant obvious, even where the change was one capable of being made from a theoretical point of view). The mere possibility for modification is not the "motivating force" that the Board and the Federal Circuit have invariably required. Accordingly, as the claimed invention is not rendered obvious in view of the Höfle reference, it is respectfully requested that this rejection be withdrawn.

Information Disclosure Statement

The Office Action states that the Information Disclosure Statement (IDS) fails to comply with 37 CFR 1.98(a) because a copy of the references cited therein have allegedly not been provided. Applicants respectfully point out that PTO Form 1449 and the corresponding references were mailed to the Patent Office on January 18, 2000. Applicants hereby provide a copy of the stamped postcard receipt wherein the Patent Office acknowledges receipt of the IDS and Form 1449 on January 20, 2000. In that the IDS, Form 1449 and copies of references cited therein were all included in the same box, it is believed that the references were, in fact, received by the Patent Office. Accordingly, the Information Disclosure Statement filed by Applicants does comply with 37 CFR 1.98(a).

Applicants also point out that the references cited in Form 1449 filed in connection with the present application are identical to those cited in connection with copending U.S. Application Serial Nos. 09/084,542; 09/170,581; 09/280,191; 09/280,192 and 09/316,796. Accordingly, the cited references may also be obtained from any of these applications. In the event, however, these cited references cannot be located, Applicants will provide an additional set, if so requested.

Applicants believe all of the claims presently before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

If any fee is due in connection herewith, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,

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Date: **December 15, 2000**

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